RELATIONSHIP OF THE PARATHYROID GLAND TO CALCIUM METABOLISM*

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THE parathyroid glands first made their appearance on the anatomic horizon about 50 years ago, Sandström being the first to recognize them as independent organs. For several years they were considered to be aberrant thyroid tissue, but in the late years of the past century the individual function of the parathyroids was finally recognized, and since that time these glands and the rôle played by their secretion in body metabolism have been of vital interest to the clinician, the research worker, and the biologic chemist. Since these glands have been classed among the organs of internal secretion, the amount of literature on the subject has been enormous. One paper on experimental work alone gives 2,600 references and another well over 500. The various theories as well as the case reports have been, to the clinician at least, most confusing. While the last word on this subject is far from being said, certain fundamentals seem to be established and this paper is an attempt on the author's part to clarify for himself the principles of calcium metabolism and the effect of parathyroid secretions on this metabolism and also to work out a practical method of diagnosis and treatment of the cases in which hyperparathyroid function occurs.

In this paper the citation of cases seen at the Orthopaedic and the Graduate Hospitals and direct references to published papers have been deliberately eliminated and the statements presented are only the personal conclusions drawn from these sources. The publication in the near future of the researches of Doctor White and Doctor Stein will give in more detail much of the data on which these conclusions are based.

One sure fact that seems to be beyond dispute is that the parathyroid hormones play their most important clinical rôle in the deposition and extraction of calcium salts in the body skeleton. To understand the pathologic problems a knowledge of the normal mechanism of calcium deposit is necessary. Bones owe their rigidity to the precipitation in them of calcium phosphate and calcium carbonate, the phosphate being by far the more important. The exact formula of this phosphatic deposit is still in question but is of no consequence to the clinician. Although the experimental data on the subject are still incomplete and often very confusing, it now seems to be a well-established fact that our old theories of the specific power of the osteoblastic cells to lay down new bone must be discarded. According to the present theories the precipitation of calcium phosphate in bone is brought about by the local chemical action of an enzyme, called by Kay and Robison phospho-

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tase, acting on the calcium and phosphorus ions found in normal body fluids that bathe the bones. All body fluids are identical as far as calcium and phosphorus are concerned and blood serum can be considered as an example. This phosphotase is probably supplied by the cells of peri- and endosteum and it is supposed to act by causing a local overproduction of phosphate. It is also supposed to become active only in the presence of another enzyme known as vitamin D.

The calcium and phosphorus ions of the blood serum are, therefore, the raw materials from which the calcium phosphate of the bone is formed. From a practical standpoint, blood serum may be considered to be a supersaturated solution of calcium and phosphorus ions. Its calcium ions can be divided into three distinct fractions. First, calcium that is normally soluble in any solution of the same composition as serum, the amount being about 2 mg. per 100 cc. of blood. Second, calcium held in solution by the parathyroid hormones present in the serum, 4 mg. per 100 cc., and third, calcium combined with protein, 4 mg. per 100 cc., making a normal total calcium content of 10 mg. The first is known as chemically dissolved calcium, and the second as biologically dissolved calcium, and the third as calcium proteinate. The first two forms are in equilibrium with phosphorus and are active in bone formation. The third form is inert and plays no part in calcification. In other words, chemically and biologically dissolved calcium are the active reservoirs of the materials for bone formation. The chemically dissolved calcium is a constant fraction but the amount of biologically dissolved calcium seems to depend on the amount of parathyroid hormone present at any given time in the blood stream.

It seems to be a primary law of body metabolism that the blood serum must always be in this state of supersaturation and that anything that destroys this condition will draw calcium or phosphorus from some other source to maintain it. To put it in another way—the amount of calcium and phosphorus in the blood stream varies with the amount of parathyroid hormone, and this hormone must be satisfied. Normally, this condition is fulfilled by the salts absorbed from the alimentary tract, but if these be deficient, the calcium and phosphorus stored in the bones can be redissolved to make up the necessary amount.

Vitamin D is another factor in maintaining the calcium-phosphorus balance in the blood. This substance is supposed to aid in the absorption of the salts from the alimentary canal in addition to its action on the phosphotase in the bone. Normally, the ingestion of these salts amounts to about one Gm. of calcium and two Gm. of phosphorus per day and a like amount is excreted, 90 per cent of the excretion taking place through the feces and 10 per cent through the urine.

The evidence now at hand as to calcium metabolism can, therefore, be summarized by these statements. First, the bone building mechanisms depend on the blood serum for their raw materials. Second, in normal blood serum there is an approximately fixed ratio between calcium, phosphorus,

parathyroid hormones and vitamin D, the normal ratio between calcium and phosphorus in the adult being about 10 to 4, and in the child about 10 to 5. Third, that any disturbance of this ratio demands an extra supply of calcium or phosphorus from some source to reestablish this ratio. Fourth, if this extra supply can be obtained from ingested salts no bone changes will appear, but if it cannot be so obtained, the reservoirs of calcium and phosphorus in the bone are called upon to supply the deficiency and decalcification makes its appearance. To state the same fact in another way, if one of the factors of this serum ratio be changed, all must be equally changed to prevent bone disturbance.

In addition to its bone forming functions, calcium together with other ions is supposed to maintain the physicochemical equilibrium necessary for normal irritability of muscles and nerves. Its especial function is to lessen irritability at the neuromuscular junctions both in the heart and in voluntary and involuntary muscle fibers.

In taking up the pathologic changes due to irregularity of parathyroid secretions, the clinical manifestations of lowered parathyroid secretion are now fairly well understood. Lowered parathyroid activity causes a marked diminution in serum calcium, but no loss of the total calcium of the body by excessive secretion, the excess calcium being stored in the spongy bone. The carpopedal spasms, general convulsions, *etc.*, which are the distinguishing signs of tetany, are due, therefore, to the lowering of the total calcium content of the blood by the marked lessening of the biologically dissolved fraction. The introduction of calcium through the alimentary canal, especially when given with a meat free diet, is of distinct use in combating this hypocalcemia and the symptoms caused by it. Of more importance is the use of parathyroid hormone. In 1924 this hormone was first extracted by Collip and has been used both experimentally and clinically. Its intramuscular injection is followed by a rapid rise in serum calcium and an increased excretion of both calcium and phosphorus with diminution of the symptoms of tetany.

The effect of hypersecretion still presents many unsolved problems and the facts presented here are drawn mainly from the experimental and clinical work done at the Orthopaedic Hospital originally by Doctor E. P. Corson White and recently by Doctors White and Stein.

The addition of excessive parathyroid hormone to the blood stream brings about an excess of calcium ions and a lowering of phosphorus. At the same time there is a marked increase in the amount of calcium and phosphorus excreted. Normally, as has been said, 90 per cent of the calcium is excreted by the alimentary canal and 10 per cent by the kidneys. In hyperparathyroid conditions this ratio is reversed and up to 90 per cent of calcium is eliminated by the kidneys and as little as 10 per cent by the alimentary canal. If this excessive calcium excretion persists, marked kidney dysfunction occurs and a marked rise in the phosphorus content of the blood is brought about. Therefore, while a high calcium and a low phosphorus value is seen in the

early stages of hyperparathyroidism, the blood picture may be entirely changed by the loss of kidney function. It is, therefore, necessary to examine the eliminating power of the kidneys in all cases in which the blood picture shows an abnormally high per cent of calcium. This extra calcium in the blood is necessarily drawn from the salts stored in the bone structures and decalcification will occur unless the normal blood balance is restored either by eliminating the causal factor or by increasing the ingestion of calcium and phosphorus from the alimentary canal. The blood picture above described is not necessarily caused by overactivity of the parathyroids—other pathologic states such as sarcoma, metastatic carcinoma, acidosis, and at times tuberculosis, will give the same picture—but the history, the clinical examination, and especially, the roentgenographic studies, will go far in clearing up the diagnosis.

The clinical symptoms of hyperparathyroidism are mainly caused by these changes in the blood, and give the clinical picture of generalized osteitis fibrosa first described by Von Recklinghausen in 1891. The serum calcium rises to 12 mg. or over. Serum phosphorus falls to 2.7 mg. or under. The urinary output is increased to the point of polyuria. Urinary and renal calculi may be found. Renal damage occurs. The muscles weaken and become easily fatigued and often painful. The gastro-intestinal tract often shows signs of irritation, leading to nausea, vomiting, or constipation. The long bones progressively decalcify, becoming thinned and distorted. Eventually fractures may occur. Bone and joint pain and inability to bear weight are early and persistent symptoms. These bone changes are fairly well distributed throughout the skeleton. The bone marrow is damaged and fibrous tissue replaces the normal cells. This fibrous change is progressive and gives rise to tumorlike masses within the bones. Cystic changes due to necroses occur, and when the fibrous tissue be invaded with giant cells, giant cell tumors will form. These giant cells can be found also in the walls of the primary cysts. Hemorrhage into these masses will give the typical brown tumors of Von Recklinghausen's disease.

Given a case in which the diagnosis of hyperparathyroidism is established, is there any quantitative test that will accurately estimate the amount of parathyroid secretion present? From an experimental standpoint such a test can be made which is known as the Hamilton test, and can be used clinically to estimate grossly the amount of parathyroid hormone present. However, we can still rely on the clinical picture plus the repeated blood tests in planning treatment.

This treatment is based on the fact that hyperparathyroid function throws into the blood stream an excessive amount of its secretion, thus destroying its normal ratio with calcium, phosphorus and vitamin D. To overcome this effective treatment must either reduce the amount of secretion or utilize the excess. Three types of treatment must be considered—surgery, roentgen ray, irradiation and diet.

Surgery when used alone is distinctly limited in its effectiveness. The

parathyroid glands vary greatly, both as to their number and their position. They can be classed in two groups—those that are developed from the third bronchial cleft, and those developed from the fourth. The first group, usually two in number, lie behind or in the substance of the thyroid gland. The second group lie along the carotids and trachea and may extend well down into the thoracic cavity. Adenomata of these glands may form and when they can be diagnosed their extirpation is, according to some case reports, of distinct value. Removal of one gland will at times give temporary relief, but the remaining glands tend to hyperplasia and secondary removals are often necessary. Reports in literature of the operative results vary so much that no definite statistics can be given. It would seem, however, that surgical extirpation alone has given permanent results in a very small percentage of cases.

Roentgen ray irradiation is still in the experimental stages. It has been shown that the activity of the glands can be temporarily or permanently diminished by the use of fractional doses given over the whole parathyroid area at three- or four-day intervals. The total dosage employed is usually about 80 per cent of the erythema dose. It has the advantage of covering the whole parathyroid bearing area, but has the disadvantage of inhibiting thyroid function at the same time. A few successful cases of its use in cystic bone disease and giant cell tumor have been reported, but the amount of the dosage and permanence of its effect have not as yet been sufficiently tested.

At the present time treatment by means of absorption from the alimentary canal seems to be the best method of combating the effects of parathyroid hyperfunction. To accurately prescribe the needed amount of calcium and phosphorus intake it is necessary to know the exact degree of negative imbalance in each individual case. That is to say, each case must be tested to determine exactly how much the calcium or phosphorus excretion exceeds the intake. Such testing can be done only with hospitalized patients and by trained technicians. The exact amount of calcium phosphorus intake and output must be measured. In the Orthopaedic Hospital this is done for three consecutive days. The number of grains of calcium and phosphorus that must be incorporated in the daily diet of the patient to overcome the excess of elimination over intake can then be estimated. Calcium chloride, calcium lactate and disodium phosphate and calcium biphosphate are the drugs usually used. To these are usually added an adequate amount of vitamin D, usually in the form of viosterol (250 D).

To sum up the treatment, accurate dietary measures to increase the calcium and phosphorus intake to a point that will restore normal ratio between these salts and the parathyroid hormone in the blood seems to offer the best method of combating hyperparathyroid secretion. Surgery and the use of the roentgen ray in properly selected cases may be of great assistance, but so far as we know now should be used as adjuncts to diet rather than as the only method of treatment.

In cases with normal kidney function the high calcium-phosphorus diet works exceedingly well. However, in those cases in which there has been marked kidney damage, operative removal of parathyroid tissue or irradiation together with a very small amount of extra calcium and phosphorus by mouth will probably save the patient from the pathologic calcification so often caused by damaged kidney.

There are at present so many side issues that are still in the controversial state that to discuss them would only befog the main picture. We can, however, hope that as experimental work goes on, and our knowledge increases, a more clearly cut and practical method of handling the whole field of faulty calcium metabolism may appear and that many of the puzzling problems, such as Paget's disease, nonunion or faulty union of fractures, the various types of rickets, osteomalacia and osteogenesis imperfecta may finally yield to an understanding use of surgery and physiologic chemistry.